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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/738,540	12/14/2000	Wyne Pun Lee	P1795R1	2012

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EXAMINER
HADDAD, MAHER M

ART UNIT	PAPER NUMBER
1644	8

DATE MAILED: 07/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/738,540	Applicant(s) LEE ET AL.	
	Examiner Maher M. Haddad	Art Unit 1644	

-- The MAILING DATE of this communication appears n the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5-8-02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 17-19* is/are pending in the application.

4a) Of the above claim(s) *10-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 17-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-9 and 17-19 are pending.

2. Applicant's election without traverse of Group I, claims 1-9 (now claims 1-9 and 17-19) in Paper No. 7, drawn to a method of treating an LFA-1 or a TNF-α mediated disorder, comprising administering to mammal in need thereof effective amounts of an LFA-1 antagonist and a TNF-α antagonist, wherein the LFA-1 antibody is CD11a and the autoimmune pathology is SLE and reheumatoid arthritis as the species, is acknowledged.

3. Claims 1-9 and 17-19 are under examination drawn to a method of treating an LFA-1 or a TNF-α mediated disorder, comprising administering to mammal in need thereof effective amounts of an LFA-1 antagonist and a TNF-a antagonist, wherein the LFA-1 antibody is CD11a and the autoimmune pathology is SLE and reheumatoid arthritis as the species.

4. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

5. Applicant's IDS, filed 07-2-01 (Paper No. 4, is acknowledged. However, the references (1-85) are crossed out as the entire documents were not found. Applicant is invited to produce such documents.

6. Claims 5-9 and 17 are objected to under 37 CFR § 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim.

7. Claim 18 is objected to because it dependents from canceled claim 10. Examiner considers newly submitted claim 18 was intended to depend from claim 9.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 8-9 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 18 is indefinite in the recitation of "the fusion protein consists of the extracellular ligand binding portion of human tumor necrosis factor receptor linked to the hinge region, CH2 domain, and CH3 domain of human IgG1" because the metes and bounds of

said "fusion protein" is unclear and ambiguous. It is unclear whether "the extracellular ligand binding portion of human tumor necrosis factor receptor" linked to the hinge, linked to CH2 domain and linked to CH3 domain of human IgG1 or "the extracellular ligand binding portion of human tumor necrosis factor receptor" linked to Fc component contains the hinge, CH2 domain and CH3 domain of human IgG1.

B) Claims 8-9 are indefinite in the recitation of "one of claim 7" and "one of claim 8" respectively because both claims 8 and 9 recite only one claim to choose from.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-8, 17 and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating rheumatoid arthritis, comprising administering to a mammal in need thereof effective amounts of an anti-CD11a antibody and a TNF-α-receptor-IgG Fc fusion protein does not reasonably provide enablement for a method of treating any LFA-1 or any TNF-α mediated disorder, comprising administering to a mammal in need thereof effective amounts of any LFA-1 antagonist and any TNF-α antagonist in claim 1; a method of treating cartilage damage for injury or preventing initial or continued damage by any degenerative cartilaginous disorder or injury, comprising contacting the cartilage with effective amounts of any LFA-1 antagonist and any TNF-α antagonist in claim 2; wherein the order is any degenerative cartilagenous disorder in claim 3; wherein the LFA-1 antagonist is any anti-LFA-1 antibody in claim 5; wherein the TNF-α antagonist is any immunoadhesin in claim 7, wherein the immunoadhesin is any fusion of at least any portion of any TNF-α binding protein and any portion of any immunoglobulin in claim 8. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification disclosure does not enable one skilled in the art to practice the invention without any undue amount of experimentation.

Besides anti-CD11a antibody and TNF-α receptor-IgG Fc fusion protein, the specification fails to provide any guidance as to how to make and how to use any "LFA-1 antagonist" and any "TNF-α antagonist".

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient

working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

Applicant has not provided sufficient biochemical information that distinctly identifies such "LFA-1 antagonist" and "TNF-α antagonist" other anti-CD11a antibody and TNF-α receptor-IgG Fc fusion protein respectively. While any LFA-1 antagonist and any TNF-α antagonist may have some notion of the activity of the "inhibitory agent", claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make such agents, commensurate in scope with the claimed invention. The specification (page 15, line 15-28, page 16, lines 1-13) fails to provide any guidance on how to make any LFA-1 antagonist, any TNF-α antagonist, any LFA-1 antibody, any portion of a TNF-α binding protein, or any portion of an immunoglobulin that can be used to treat rheumatoid arthritis in mammal.

There is insufficient guidance as to which amino acid portions within the receptor can be unique and retain a distinct functional capability of TNF-α receptor polypeptide. Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Since the amino acid sequence of a polypeptide determined its structural property, predictability of which amino acid portion can retain the functional capabilities of the TNF-α receptor requires knowledge of, and guidance with regard to, which portions in the polypeptide contribute to its function.

Minor structural differences among structurally related compounds or compositions can result in substantially different biological activities. Therefore, structurally unrelated compounds comprising any "TNF-α antagonist"" would be expected to have greater differences in their activities.

Therefore, there is insufficient direction or objective evidence as to how to make and to how to use any LFA-1 antagonist and any TNF-α antagonist which treats rheumatoid arthritis for the number of possibilities associated with the myriad of direct and indirect effects associated with various "antagonist" and, in turn, as to whether such a desired effect can be achieved or predicted, as encompassed by the claims.

Also, an effective treatment protocol for treating an LFA-1 or a TNF-α mediated disorder in a mammal is subject to a number of factors which enter the picture beyond simply the administration of anti-CD11a antibodies, TNF-α receptor-IgG Fc fusion protein and methotrexate to a mammal. Van Noort et al. (International Review of Cytology, 1998) indicate factors that effect autoimmune disease such as genetic, environmental and hormonal (Page 127, Paragraph 1). LFA-1 or a TNF-α mediated disorder is subject to variables beyond administration of anti-CD11a antibodies, TNF-α receptor-IgG Fc fusion protein and methotrexate to the mammal. The ability of a host to suppress and thereby treat inflammatory joint disorder after establishing itself will vary depending upon factors such as the condition of the host and burden of LFA-1 or a TNF-α mediated disorder. Therefore, it is not clear that the skilled artisan could predict the efficacy of the "anti-CD11a antibodies, TNF-α receptor-IgG Fc fusion protein and methotrexate" exemplified in the specification. *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

10. Claims 1-8, 17 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a method of treating rheumatoid arthritis, comprising administering to a mammal in need thereof effective amounts of an anti-CD11a antibody and a TNF-α-receptor-IgG Fc fusion protein.

Applicant is not in possession of a method of treating any LFA-1 or any TNF-α mediated disorder, comprising administering to a mammal in need thereof effective amounts of any LFA-1 antagonist and any TNF-α antagonist in claim 1; a method of treating cartilage damage for injury or preventing initial or continued damage by any degenerative cartilaginous disorder or injury, comprising contacting the cartilage with effective amounts of any LFA-1 antagonist and any TNF-α antagonist in claim 2; wherein the order is any degenerative cartilagenous disorder in claim 3; wherein the LFA-1 antagonist is any anti-LFA-1 antibody in claim 5; wherein the TNF-α antagonist is any immunoadhesin in claim 7, wherein the immunoadhesin is any fusion of at least any portion of any TNF-α binding protein and any portion of any immunoglobulin in claim 8.

Applicant has disclosed only anti-CD11a antibody and TNF-α-receptor-IgG Fc fusion protein; therefore, the skilled artisan cannot envision all the contemplated

antagonist possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

12. Claims 1-6 and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,037,454, as is evidenced by Genentech: News Release Thursday, Jun 21, 2001.

The `454 patent teaches humanized anti-CD11a antibodies that can be administered to mammal concurrently with an immunosuppressive agent such as anti-tumor necrosis factor-α antibodies to treat LFA-1 mediated disorder such as rheumatoid arthritis (column 4 lines 35-67 and column 5, lines 1-37 in particular).

Claim 6 is included, because the reference anti-CD11a antibodies are the same as the claimed anti-CD11a antibodies. Therefore, the anti-CD11a antibody inherent would be a non T-cell depleting antibody.

Further, as is evidenced by Genentech News Release, patients receiving Xanelim, an anti-CD11a humanized monoclonal antibody, did not experience T-cell depletion (page 1, paragraph 7 in particular).

The reference teachings anticipate the claimed invention.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 7-9 and 18-19 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 6,037,454, in view of U.S. Patent No. 6,306,820 or in view of the known fact disclosed in the specification on page 16, line 5 and page 17, lines 4-5.

The teachings of the `454 patent have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation that the TNF-α antagonist is an immunoadhesin in claim 7, the immunoadhesin is a fusion of at least a portion of a TNF-α binding protein and a protein of an immunoglobulin in claim 8, the TNF-α binding

protein is a TNF-α receptor-IgG Fc fusion protein in claim 9, the fusion protein consists of the extracellular ligand binding portion of human tumor necrosis factor receptor linked to the hinge region, CH2 domain, and CH3 domain of human IgG1 in claim 18 and the method of treating an LFA-1 or a TNF-α mediated disorder, further comprising administering to the mammal an effective amount of methotrexate in claim 19.

The `820 patent teaches the ability of TNFbp product(s) (e.g., sTNFR-I, sTNFR-II, sTNFR fragments (2.6 D sTNFRs such as 2.6 D sTNFR-I) or sTNFR Fc(s) (sTNFR-I/IgG1 or sTNFR-II/IgG1) and methotrexate to act synergistically in the treatment of various symptoms associated with TNF-mediated diseases, including acute and chronic inflammation such as rheumatic diseases. The `820 patent further teaches the amino-terminal or carboxy-terminal fusion of a TNFbp(s) with all or part of the constant domain of the heavy or light chain of human mmunoglobulin (individually or collectively, ("sTNFR Fc(s)"). Such chimeric polypeptides are preferred wherein the immunoglobulin portion of each comprises all of the domains except the first domain of the constant region of the heavy chain of human immunoglobulin such as IgG (e.g., IgG1 or IgG3) (column 6, lines 56-65 in particular). Finally, the `820 patent teaches that the combined treatment with TNFbp product(s) and methotrexate has the advantage of achieving the same result with a lower dose or less frequent administration of methotrexate, thereby reducing any toxic effect (column 35, lines 47-67 and column 36, line 1-2 in particular).

As is evidenced in the specification on page 17, lines 4-5, that the claimed TNF-α antagonist is a TNF-α receptor –IgG Fc fusion protein, such as ENBREL (Immunex) is known. ENBREL consists of the extracellular ligand-binding portion of the tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1. The Fc component of ENBREL contains the CH2 domain, the CH3 domain and hinge region (page 3, lines 6-9 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the well known ENBREL as is evidenced in the specification on page 17, lines 4-5, or TNF-α receptor -IgG Fc fusion protein in combination with methotrexate taught by the `820 patent with anti-TNFα antibodies taught by the `454 patent in a method of treating rheumatoid arthritis.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because immunoadhesin exploit both the natural affinity of a receptor for its ligand and the effector functions of the immunoglobulin Fc region. Also, the combined treatment with sTNFR Fc(s) and methotrexate has the advantage of achieving the same result with a lower dose or less frequent administration of methotrexate, thereby reducing any toxic effect taught by the `820 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
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July 15, 2002

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